PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 11 May 2000 (11.05.00)	
International application No. PCT/US99/20047	**Applicant's or agent's file reference** 5525-0038.41
International filing date (day/month/year) 31 August 1999 (31.08.99)	**Priority date** (day/month/year) 04 September 1998 (04.09.98)
Applicant BRENNER, Sydney	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

29 March 2000 (29.03.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Pascal Piriou
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/20047

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :C12Q 1/68; C12P19/34; C12N 15/63
US CL :435/6,91.2, 440, 445, 471, 320.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/6,91.2, 440, 445, 471, 320.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,376,526 A (BROWN et al) 27 December 1994, columns 5-7.	1-8
A, P	US 5,876,941 A (LANDEGREN et al) 02 March 1999, columns 7-8.	1-8
X - A	US 5,595,895 A (MIKI et al) 21 January 1997, columns 11-13, figures 3-4.	9-11 ----- 12-16

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 02 DECEMBER 1999	Date of mailing of the international search report 14 JAN 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer D. Lawrence for CARLA MYERS Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)★

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/20047

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

DERWENT PATENTS; DIALOG: MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH
search terms: mismatch, polymorphism, heteroduplex, nuclease, exonuclease, resolvase, stuffer fragment, cloning vector, restriction enzyme/endonuclease, extend/polymerize/terminal transferase

6. The method of claim 5 wherein said single stranded DNA of said test DNA population is generated by amplifying said members of said test DNA population in a polymerase chain reaction using a nuclease-resistant primer specific for said fourth primer binding site and a primer specific for said fifth primer binding site to form an amplicon having a single strand with a nuclease-resistant 5' end, and digesting the amplicon with a 5'→3' exonuclease.

7. The method of claim 2 wherein said step of forming a population of heteroduplexes includes partitioning said test DNA population into subpopulations and separately forming subpopulations of heteroduplexes from single stranded DNA of said reference DNA population and single stranded DNA from each subpopulation of said test DNA population.

8. The method of claim 7 wherein said subpopulations of said test DNA population and said reference DNA population have complexities which permit at least ninety percent of heteroduplexes of said subpopulations of heteroduplexes to be formed in seventy-two hours or less.

9. A cloning vector for incorporation of DNA digested by a restriction endonuclease, the cloning vector comprising the following sequence of elements:

a first restriction endonuclease recognition site;

a stuffer fragment; and

a second restriction endonuclease recognition site, the first and second restriction endonuclease recognition sites being specific for restriction endonucleases selected from the set consisting of type IIs restriction endonucleases and type II restriction endonucleases recognizing interrupted palindromic sequences.

10. The cloning vector of claim 9 wherein said first restriction endonuclease recognition site and said second restriction endonuclease recognition site are the same.

11. The cloning vector of claim 10 wherein said first restriction endonuclease recognition site and said second restriction endonuclease recognition site are selected from the group consisting of Sap I, Ear I, Ksp632 I, Mwo I, Blp I, Bsu36I, Dde I, Hinf I, EcoO109 I, and Sau96 I.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
5525-0038.41		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/20047	31 AUGUST 1999	04 SEPTEMBER 1998

International Patent Classification (IPC) or national classification and IPC
IPC(7): C12Q 1/68; C12P 19/34; C12N 15/63 and US Cl.: 435/6,91.2, 440, 445, 471, 320.1

Applicant
LYNX THERAPEUTICS, INC.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

- I [X] Basis of the report
- II [ ] Priority
- III [ ] Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV [ ] Lack of unity of invention
- V [X] Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI [ ] Certain documents cited
- VII [ ] Certain defects in the international application
- VIII [ ] Certain observations on the international application

Date of submission of the demand	Date of completion of this report
29 MARCH 2000	05 DECEMBER 2000
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer Dorothea Lawrence for CARLA MYERS
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

Form PCT/IPEA/409 (cover sheet) (July 1998)★

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/20047

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed

☒ the description:
pages (See Attached) , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

☒ the claims:
pages (See Attached) , as originally filed
pages _____ , as amended (together with any statement) under Article 19
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

☒ the drawings:
pages (See Attached) , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

☒ the sequence listing part of the description:
pages (See Attached) , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the writen sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

☒ the description, pages NONE

☒ the claims, Nos. NONE

☒ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

***Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/20047

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	**Claims**	1-8, 11-16	**YES**
	Claims	9-10	**NO**
Inventive Step (IS)	**Claims**	1-8, 11-16	**YES**
	Claims	9-10	**NO**
Industrial Applicability (IA)	**Claims**	1-16	**YES**
	Claims	NONE	**NO**

2. citations and explanations (Rule 70.7)

Claims 9-10 lack novelty under PCT Article 33(2) as being anticipated by Miki et al (herein after 'Miki'). Miki teaches cloning vectors which comprise a first and a second restriction endonuclease site, wherein a removable fragment of DNA (i.e. a "stuffer fragment")is present between the first and second restriction endonuclease sites and cleavage of the DNA with the restriction endonuclease results in the release of the "stuffer fragment"(see columns 11-13). For example, the vectors may contain a first and a second restriction enzyme site that is cleavable by the type II restriction endonuclease SfiI. Miki further discloses vectors in which the sequence of the vector at the first and second restriction endonuclease sites are identical (see column 5). In particular, the restriction endonuclease site is BstXI and a "short, replaceable segment of DNA" is present between the first and second restriction endonuclease sites.

In the response filed 10 October 2000, it is stated that the claims have been amended so that they are limited to cloning vectors comprising sites for "type II restriction endonucleases (which cleave DNA at a site other than their recognition sequence)". However, the claims have been amended to broadly recite vectors comprising sites for any type II restriction endonuclease. The claims do not require type II restriction endonucleases that cleave only at a site other than their recognition sequence. Because "type II restriction endonucleases" include both endonucleases which cleave at their recognition sequence and endonucleases which cleave at a site other than their recognition sequence, the claims are inclusive of the vectors of Miki et al which comprise the type II restriction endonuclease sites SfiI and BstXI.

Claims 1-8 and 11-16 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest methods for cloning a restriction fragment wherein the methods comprise providing a population of restriction fragments, each end of the restriction fragment having a recessed 3' end and protruding 5' end, extending the 3'recessed end by one nucleotide to generate a modified restriction fragment, providing a vector (Continued on Supplemental Sheet.)

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

I. BASIS OF REPORT:

This report has been drawn on the basis of the description,
page(s) 1-14, as originally filed.
page(s) NONE, filed with the demand.
and additional amendments:
NONE

This report has been drawn on the basis of the claims,
page(s) 15 and 17, as originally filed.
page(s) NONE, as amended under Article 19.
page(s) NONE, filed with the demand.
and additional amendments:
Claim page 16, filed with the letter of 10 October 2000.

This report has been drawn on the basis of the drawings,
page(s) 3, as originally filed.
page(s) NONE, filed with the demand.
and additional amendments:
Pages 1, 2 and 4, filed with the letter of 10 October 2000.

This report has been drawn on the basis of the sequence listing part of the description:
page(s) NONE, as originally filed.
pages(s) NONE, filed with the demand.
and additional amendments:
NONE

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):
with a first and second restriction endonuclease site and a removable stuffer fragment, digesting the vector with an enzyme which recognizes the first and second restriction endonuclease sites to generate a linear vector with ends complementary to those of the modified restriction fragment and inserting the modified restriction fragment into the linear vector. Furthermore, the prior art does not teach or suggest methods for detecting polymorphic DNA sequences wherein the methods comprise forming a population of heteroduplexes comprising a single stranded DNA from a reference population and a single stranded DNA from a test population, isolating mismatched heteroduplexes by digesting one of the strands of the DNA from each of the perfectly matched duplexes thereby leaving double-stranded mismatched DNA, amplifying the isolated double-stranded mismatched DNA and determining the nucleotide sequence of the amplified mismatched DNA.

---------- NEW CITATIONS ----------
NONE